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1. Current literature highlights

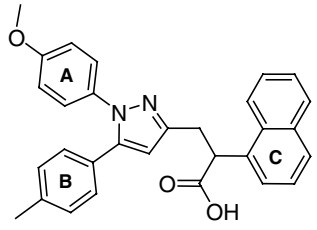
1.1. Pyrazole CCK_1 receptor antagonists

Cholecystokinin (CCK) is an endogenous 33 amino acid peptide hormone first identified by its pharmacological actions early in the last century, and later purified and sequenced in the 1970s. Subsequently, it was shown that CCK was released in response to food intake and that it regulates gallbladder contraction, pancreatic enzyme secretion, gastric acid secretion, and colonic motility amongst other pharmacological effects. CCK is abundant in the CNS and is believed to be involved in aspects of nociception, satiety and anxiogenesis.

The biological actions of CCK are mediated through two G-protein coupled receptors, CCK_1 and CCK_2, and a number of CCK_1 antagonists have been evaluated in the clinic for pancreatic disorders, IBS and biliary colic. Encouraging clinical results from a phase II trial of constipation-dependent IBS with a peptide derived CCK_1 antagonist has given encouragement to pursue non-peptide antagonists of CCK_1.[1]

In this recent work, efforts were undertaken to modify an HTS lead (i) that was identified as a potent and selective antagonist of the CCK_1 receptor (pK_i 7.6). This compound displayed promising physical properties and represented a novel chemical scaffold for SAR investigations undertaken by the construction of a solution phase library. The synthetic scheme involved varying positions around aromatic centers B and C giving antagonists of CCK_1 with pK_i values between 6.2 and 8.1.

During the course of these studies, a novel method for the evaluation of SAR in combinatorial matrices was explored. This new methodology provided for a quantitative assessment of additive and non-additive relationships in the SAR, allowing one to identify potential changes in the binding modes of these antagonists. The assumption with additive SAR models is that one variable in the structure does not affect the binding or conformation of the second variable. However, in many documented cases this assumption is invalid, thus limiting the predictive power of additive models. With the advent of combinatorial methods, a full matrix of compounds can be readily accessed synthetically, and the presence of non-additive relationships in the full matrix can suggest either a different binding mode in the biological target or direct interactions between different parts of a ligand. The results from this study indicate that all compounds tested bind to the receptor in a similar binding mode.



(i)

1.2. Aminopyrrolidinetricarboxylic acids: new group III metabotropic glutamate receptor-selective antagonists

The glutamate neurotransmitter plays a critical role in many disease processes. Glutamate exerts its effects through two families of receptors: metabotropic (mGlu) and ionotropic (iGlu) receptors. mGlu receptors have been further divided in three groups according to their sequence homologies, pharmacological properties and signal transduction pathways.

Group III mGlu receptors include mGlu4, mGlu6, mGlu7 and mGlu8 receptors, which are negatively coupled to cAMP production. So far, only a few orthosteric ligands, that compete with glutamate, have been described for

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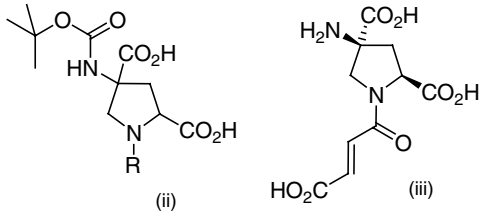
group III mGlu receptors. Typically, these agonists have low-micromolar to sub-micromolar potencies for mGlu4, mGlu6 and mGlu8, whilst displaying much less potency at the mGlu7 receptor. Recent work has demonstrated the utility of parallel chemistry for the rapid synthesis of polar amino acid derivatives that are orthosteric agonists of group III mGlu receptors.[2]

This work focuses on aminopyrrolidine-tricarboxylic acid (APTC) derivatives based on a family of APTCs known to provide selective group III agonists. The aim was to have a rigid template which would allow for the placement of polar functionality around the core, thus encouraging interaction of these polar groups with distal binding pockets in the receptors. Following solution phase synthesis of diastereoisomerically-pure protected cores, exemplified by generic structure (ii), a library of 65 compounds was constructed in solution resulting from capping of the pyrrolidine nitrogen with various (R)-groups, followed by deprotection of the Boc protecting-group. The nitrogen was capped with electrophilic reagents using solid supported reagents and scavengers.

The compounds prepared were screened against three group III mGlu rat receptors (mGlu4, mGlu6 and mGlu8) for their agonist and antagonist activities at 450 μM and 300 μM, respectively. One of the most potent compounds obtained was (iii) which displayed an agonist response to mGlu4 with an EC_{50} of 48 μM. This compound displayed 7-fold selectivity against mGlu6 and was equally active against mGlu8. Compound (iii) was inactive ($EC_{50} > 5000$ μM) against group I receptors (mGlu1, mGlu5) and the group II receptor mGlu2. Interestingly, compound (iii) is a full agonist for mGlu4 but a partial agonist for mGlu8, despite it having a similar EC_{50} value against both mGlu4 and mGlu8.



(ii)

(iii)

2. A summary of the papers in this month's issue

2.1. Solid-phase synthesis

A general and efficient solid-phase synthesis of N-9-substituted 2,8-diaminopurines from 5-nitrouracil has been described. The key synthetic transformation employs a carbodiimide-mediated cyclisation of a thiourea.[3]

The solid-phase synthesis of fused [2,1-*b*]quinazolinone alkaloids has been developed for the preparation of vasicinone and deoxyvasicinone by two alternative approaches.[4]

A new method for the preparation of peptide thioester by the post-solid phase peptide synthesis (SPPS) approach has been developed. A series of *N*-alkyl cysteine derivatives were prepared and used as the C-terminus residue of the peptides prepared by the Fmoc SPPS, and the synthetic peptides released from resin by TFA were readily converted to the peptide thioester without significant side reactions.[5]

A method to transform allyl esters to thioesters under solid phase conditions has been developed to synthesise peptide thioesters.[6]

A microwave-assisted traceless rapid synthesis of benzimidazolones on polymeric supports has been developed.[7]

Two novel microgonotropens (MGTs) comprised of hairpin *N*-propylaminepyrrole polyamides linked to a Hoechst 33258 (Ht) analogue have been synthesised on solid phase by adopting an Fmoc technique using a series of HOBt mediated coupling reactions.[8]

2.2. Solution-phase synthesis

Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid, five aldehydes and two isocyanides were reacted both in methanol and in water to prepare a 10-membered *β*-lactam library via an Ugi-4-centre-3-component reaction.[9]

The concept, protocols and instruments of fluorous solid-phase extraction techniques, and their applications for solution-phase parallel and high-throughput synthesis of small molecules and biomolecules have been reviewed.[10]

Nucleophilic addition of Grignard or lithiated reagents to new Weinreb amides efficiently gave the corresponding ketones and allowed the design and synthesis of a new indazole library.[11]

A rapid library-generation via liquid-phase multiple-parallel synthesis of 2-(substituted)benzyl-1-benzopyrano[4,3-*c*]-pyrazol-3(2*H*)-ones, bearing two points of diversity, under microwave irradiation has been successfully performed using chromenone-3-carboxylic acids as starting materials. Compared to an identical library generated by conventional parallel synthesis, microwave-assisted parallel synthesis dramatically decreased reaction times from an average of 16 h to 13 min, and the yields of products and intermediates were improved in most cases.[12]

2.3. Scaffolds for combinatorial libraries

The synthesis of a 5,7-dichloropyrido[4,3-*d*]pyrimidine scaffold has been described. The chlorine at position 5 can selectively be displaced by different palladium-catalyzed cross-coupling reactions and nucleophilic aromatic substitutions. In the subsequent step, the chlorine at position 7 can be further derivatised, allowing for the construction of a diverse pyrido[4,3-*d*]pyrimidine library with structural variations at positions 5 and 7.[13]

2.4. Solid-phase supported reagents

The application of a 'catch and release' approach to palladium-catalysed multi-component cascade reactions leads to

diverse libraries of pharmacologically interesting small molecules in high yield and with excellent purity.[14]

Polymer-supported methyltrioxorhenium (MTO) systems are efficient catalysts for the oxidative functionalisation of cyclohexane and cyclopentane derivatives with H_2O_2 as oxygen donor.[15]

2.5. Novel resins, linkers and techniques

A solid macroporous monolith is shown to be a suitable substrate for anchoring a palladium complex to obtain a continuous porous material suitable for conducting flow-through catalysis in capillary microreactors.[16]

Straightforward syntheses of two *tert*-alkoxysilyl chloride functionalised resins that allow facile attachment of 1°, 2°, 3° alcohols and phenols to the solid-phase have been achieved.[17]

2.6. Library applications

A novel bacterial transcription/translation (TT) inhibitor has been identified through a combination of high throughput screening and exploratory medicinal chemistry. Initial optimisation of an anthranilic acid moiety and sulphonamide amine diversity was accomplished via one- and two-dimensional solution phase libraries.[18]

Solid-phase synthesis of a small combinatorial library of dihydroceramide analogues as mixtures of *erythro* and *threo* diastereomers has been described. Some dihydroceramide analogues cause growth arrest and apoptosis in a dose-dependent manner in human alveolar epithelial cells.[19]

The design and parallel synthesis of 217 compounds based on a malonic–hydroxamic acid template has been reported. These compounds are obtained via a two-step solution-phase procedure, and the diverse building-blocks used makes this strategy suitable for the search for inhibitors of various metallo-proteases and for the investigation of the biological role of new metallo-proteases.[20]

T-type calcium channel is one of therapeutic targets for the treatment of cardiovascular diseases and neuropathic pains. A small molecule library of dioxoquinazoline carboxamide derivatives containing 155 compounds was designed, synthesised, and biologically evaluated for T-type calcium channel blocking activity.[21]

Cu(I)-catalysed 'click' cycloaddition reactions between azides and alkynes have been employed to generate two sequential libraries of protein tyrosine phosphatase (PTP) inhibitors. Products were screened against the *Yersinia* PTP and PTP1B, and four compounds were selected and evaluated in pure form against the *Yersinia* PTP, PTP1B, TCPTP, LAR and CD45.[22]

A small library with more than forty diverse analogues of Oenostacin, a naturally occurring potent antibacterial phenolic acid derivative, have been prepared through solution phase synthesis. Some of these analogues possessed potent antibacterial activities against *Staphylococcus epidermidis* and *Staphylococcus aureus*.[23]

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